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MESTRADO INTEGRADO EM MEDICINA

Laboratório de Farmacologia Clínica e Terapêutica

Palliative Care in Heart Failure: *a systematic review of registered clinical trials*

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Catarina Manuel Borges e Gonçalves da Silva

Orientado por:

Professor Doutor Daniel Caldeira

Resumo

Título: Cuidados Paliativos em Insuficiência Cardíaca: Revisão Sistemática de ensaios clínicos registados

Introdução: A insuficiência cardíaca avançada caracteriza-se por elevada dificuldade no controlo sintomático, apesar da otimização da terapêutica convencional, e exibe uma elevada taxa de uso dos serviços de saúde nos 30 dias que antecedem a morte, tal como elevadas taxas de morbilidade e mortalidade. Assim, é de se esperar que cuidados paliativos adequados no contexto da insuficiência cardíaca se revelem benéficos no controlo dos sintomas da doença e na melhoria dos outcomes clínicos. Até ao momento a evidência científica corrobora a melhoria dos resultados centrados no doente por meio de cuidados paliativos na insuficiência cardíaca, a saber, qualidade de vida e carga de sintomas. Ainda assim a hetogeneidade dos resultados e a carência por evidência científica mais consistente, torna pertinente o estudo desta problemática.

Objetivo: Nesta revisão procedeu-se a uma avaliação transversal das intervenções e dos resultados dos cuidados paliativos estudados em ensaios clínicos registados, para abordar as lacunas no conhecimento atual.

Métodos: Para o objetivo desta revisão, foi realizada uma pesquisa de estudos registados, publicados ou não, em cada uma das bases de dados clinicaltrials.gov, WHO ICTRP, clinicaltrialsregister.eu, registro ISRCTN, seguida pela exclusão dos estudos duplicados e seleção dos relevantes de acordo com seu título e resumo. Após a leitura de cada um dos protocolos de ensaios, foi conduzido um segundo processo de selecção para excluir os ensaios que não obedeciam aos critérios de inclusão pré-definidos. Um total de 31 ensaios clínicos foram incluídos na revisão sistemática.

Resultados e Discussão: Interesse recente na implementação de intervenções de cuidados paliativos primários. A maioria das intervenções foi prestada em regime de ambulatório (48,39%; 15) e no domicílio (25,81%; 8) ou numa combinação de ambos (19,35%; 6). Do conjunto de intervenções, o contacto humano (67,74%; 21) foi privilegiado, mas o uso do telefone (3,23%; 1) e do software (6,26%; 2) como meio de prestação dos cuidados em questão começou a surgir. As intervenções apresentam uma grande heterogeneidade no método e tipo de intervenção de cuidados paliativos prestados e uma grande variabilidade

dos resultados avaliados. Os resultados mais frequentemente avaliados foram a qualidade de vida (83,87%; 26), a depressão/ansiedade (67,74%; 21) e o grau de incapacidade (61,29%; 19). Os domínios alvo diferiram entre os grupos de estágios "anteriores" e "avançados" de insuficiência cardíaca, mas ambos revelaram um grande foco no manejo dos sintomas (94,12%; 12 vs 80%; 8). Dezasseis (51,61%) dos ensaios clínicos foram publicados e 75% das publicações ocorreram após o ano de 2015.

Conclusão: Mais da metade dos estudos foram publicados nos últimos quatro anos, o que reforça a popularidade recente do tema discutido. Foi demonstrado um interesse recente pelos cuidados paliativos primários, o que pode ser explicado por uma implementação mais precoce dos cuidados paliativos no tratamento da insuficiência cardíaca. Os contextos terapêuticos mais populares foram o contexto de ambulatório e domiciliar ou uma combinação de ambos e o contato humano foi privilegiado. As várias intervenções de cuidados paliativos revelaram uma grande variabilidade de resultados e apresentam uma grande heterogeneidade no método e no tipo de intervenção de cuidados paliativos prestados. O principal domínio dos cuidados paliativos visado pela maioria dos ensaios foi a gestão sintomática. As intervenções dirigidas a doentes com insuficiência cardíaca avançada revelaram uma maior inclusão dos cuidados no final da vida/planeamento dos cuidados paliativos e componente social nas intervenções fornecidas. Concluindo, há atualmente uma mudança na abordagem dos cuidados paliativos no manejo da insuficiência cardíaca, com maior foco em uma implementação mais precoce deste tipo de cuidados.

O Trabalho Final exprime a opinião da autora e não da FML.

Palliative Care in Heart Failure: Analysis of registered clinical trials

Abstract

Background: Advanced heart failure, due to its high rate of acute service utilization in the 30 days before death and difficulty in symptomatic control, is a potential target for palliative care interventions. Previous studies in heart failure showed positive results in patient-centered outcomes using a palliative care approach. However, currently remains to be defined the optimal model of delivery, the time of referral and the criteria to select the patients in greatest need.

Purpose: To summarize and critically appraise palliative care interventions and outcomes in heart failure studied in registered clinical trials.

Study design: Systematic review

Methods: For the aim of this review, it was conducted a search of registered studies, published or unpublished, from 2000 to 2018 in the following databases clinicaltrials.gov, WHO ICTRP, clinicaltrialsregister.eu and ISRCTN registry.

Results: A total of 31 clinical trials were included in the systematic revision. Most of the interventions was provided in outpatient setting (48,39%; 15) and home setting (25,81%; 8). From the pool of interventions, the human contact (67,74%; 21) was privileged. The outcomes more frequently assessed were the quality of life (83,87%; 26), depression/anxiety (67,74%; 21) and the degree of disability (61,29%; 19). The domains targeted differed between the groups of "earlier" and "advance" stages of heart failure, but both revealed a great focus on symptoms management (94,12%; 12 vs 80%; 8). Sixteen (51,61%) of the clinical trials were published and 75% of the publications occurred after the year 2015.

Conclusion: There is currently a shift in the palliative care approach in the management of heart failure, with greater focus on an earlier implementation of this type of care, through the provision of basic palliative care and with prioritization of the outpatient and home-based setting.

Keywords: heart failure; palliative care; end of life care.

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Introduction

Palliative care is defined as an intervention whose main goal is the relief of suffering by means of pain management and physical, psychological and spiritual interventions, and improvement of the quality of life through the interdisciplinary care of patients and families facing a life-threatening illness (1). The proof collected so far supports an association between palliative care interventions and a gain in the quality of life, reduction of symptoms' burden and improvement of the caregiver's outcomes (2) (3), as well as, a greater cost-effectiveness of the health care service provided in the several settings (4) (5) (6).

When palliative care started to be implemented it was mainly directed to end-stage patients. Nowadays, early palliative care is encouraged by the World Health Organization and by the Clinical Practice Guidelines for Quality Palliative Care. There is strong evidence that supports the integration of palliative care early in the course of the disease and demonstrates an association with improvement of patient's quality of life (1) (7) (8) (9) (10) (11) (12) (13) (14) (15), as well as, with less aggressive care at end-of life (16) (17) (18) (19). Nevertheless, the optimal time of referral is yet to be defined.

Despite the optimization of conventional therapy, advanced heart failure exhibits great difficulty in symptomatic control and, when compared to cancer, exhibits a higher use of acute services in the 30 days prior to death, as well as a higher rate of mortality during hospitalizations (20). Kavalieratos et al and Xu et al, as well as others systematic reviews, reported consistent evidence supporting the improvement of patient centered outcomes by palliative care in heart failure (21) (22) (23). However, both McIlvennan & Allen and Xie et al, dated from 2016, mentioned a suboptimal incorporation of palliative care in heart failure management, mainly as a result of lack of research on this subject, limited evidence base and uncertainty in the trajectory of the disease (24) (25).

Therefore, we aim to summarize and critically appraise the available evidence on palliative care interventions and outcomes studied in registered clinical trials.

Methods

Literature Search

For the aimed of this review, registered studies, published or unpublished, from 2000 to 2018 were searched in the following databases: clinicaltrials.gov; WHO ICTRP; clinicaltrialsregister.eu; ISRCTN registry. The keywords used were palliative care or end of life and heart failure.

Study Selection

Firstly, the studies were selected according to the information included in their title and abstract. Then a second process of selection was conducted using the full-text information of each of the clinical trials, in order to exclude the trials which did not obey to the pre-defined inclusion criteria.

This review considers controlled studies that include patients with chronic heart failure, without regard to the clinical stage of the disease. For the interest of this systematic review, chronic heart failure defined at least as one of the following criteria: class I, II, III and IV of the New York Heart Association or class B, C and D of American College of Cardiology Foundation/American Heart Association or terminal care phase/end-stage heart failure, whose clinical indicators include, despite maximal treatment, renal impairment, hypotension, persistent oedema, fatigue, anorexia.

This review considers studies that evaluate the models and methods of palliative care intervention in the outcome's optimization of advanced heart failure, having been included the studies whose intervention was referred as palliative care, hospice care, comfort care, supportive care, advanced care, pain and palliative care service. Given the World Health Organization's definition of palliative care (1), the current tendency to start incorporating rehabilitation services into palliative care and the recommendation of cardiac rehabilitation by several heart failure guidelines directives, (28) (29) (30), the clinical trials which provided a service of rehabilitation were included in this systematic review.

All the studies that include evaluating specific niches of heart failure patients, such as hypertrophic cardiomyopathy, restrictive cardiomyopathy or right ventricle arrhythmogenic cardiomyopathy were not included. We considered that these patients are not representative of the commonest final pathway of cardiovascular diseases with

myocardial involvement, which is the systolic ventricular dysfunction. Studies that evaluate concomitantly participants with other advanced chronic diseases were excluded.

The studies whose main intention was to treat the disease were excluded. Studies evaluating devices as primary interventions without a multidisciplinary approach were excluded. Similarly, the ones that studied the use of inotropic drugs were excluded, as the primary mechanism relies on the improvement of myocardial contractility and not direct symptoms management.

Data extraction

The following information was extracted from the included studies: corresponding author; registration time; last update time; type of study; study phase; status; study design; number of study arms; investment source; country; sample size; baseline characteristics of participants (age; NYHA classification); eligibility criteria; outcomes, which were reported as a combination of the primary and the secondary outcomes (quality of life; complaints of pain; depression/anxiety; pulmonary and respiratory function and symptoms; cardiac function and other laboratorial parameters; oedeme and fatigue; mortality parameters; frequency of usage of health services; emotional well-being; goals of care at end of life or advance care directives; quality of communication; degree of disability; adherence to protocol; patient understanding of prognosis and perceived level of disease; patient's degree of satisfaction; patient self-care ability; patient's social limitations; caregiver burden, mood, QoL; treatment's adverse effects; nutritional, sleep and health status; cost-effectiveness of the intervention; insight on social support; participation in decision making; health literacy; time until medical optimization).

Regarding the interventions of the clinical trials, the following characteristics were defined and extracted:

- Timing of integration of palliative care:
  - NYHA staging was used has an indicator of this variable. Despite not being an unidirectional classification and not reflecting precisely the degree of progress of the disease, NYHA staging is an adequate measure of severity.
  - “Earlier stages” group, which included all the clinical trials that included as study population patients in NYHA staging I and II, as well the remaining staging.

- "Advance stages" group, which included exclusively patients in NYHA III or IV.

- Degree of expertise of palliative care that can be divided in 3 levels (31) (32):
  - Primary palliative care, which corresponds to basic palliative care that might be provided by any health care professional and integrates palliative care social worker and rehabilitate care.
  - Secondary palliative care that refers to consultation and specialized care provided by a palliative care specialist or organization.
  - Tertiary palliative care is provided often by academic medical centers in the form of intensive supportive care in the most complex patients.
- Clinical setting where the care is provided, notably ambulatory palliative care clinics, home based palliative care, inpatient palliative care consultations and inpatient palliative care units.
- Provider
- Proximity of the intervention
- Domains of the palliative care interventions:
  - Following the organization of palliative care of the 4th edition of the National Consensus Project's Clinical Practice Guidelines for Quality Palliative Care (33), we identified eight main domains of the palliative care interventions: management of physical symptoms; management of psychological symptoms; social domain; end of life care/ advance care planning; spiritual and existential approach; structure and process / care coordination; educative domain; ethical and legal aspects.

Data Analysis

The statistical analysis was performed using the Excel Office 365 for Windows. All the values showed in the results represent sums, percentages and means, unless otherwise stated. Statistical summary measures such as arithmetic mean and median were used to characterize the population. Standard deviation (SD) and interquartile range were used to evaluate data dispersion.

Results

The electronic and hand searches identified 269 citations. After full-text assessment for eligibility, 31 studies were included.

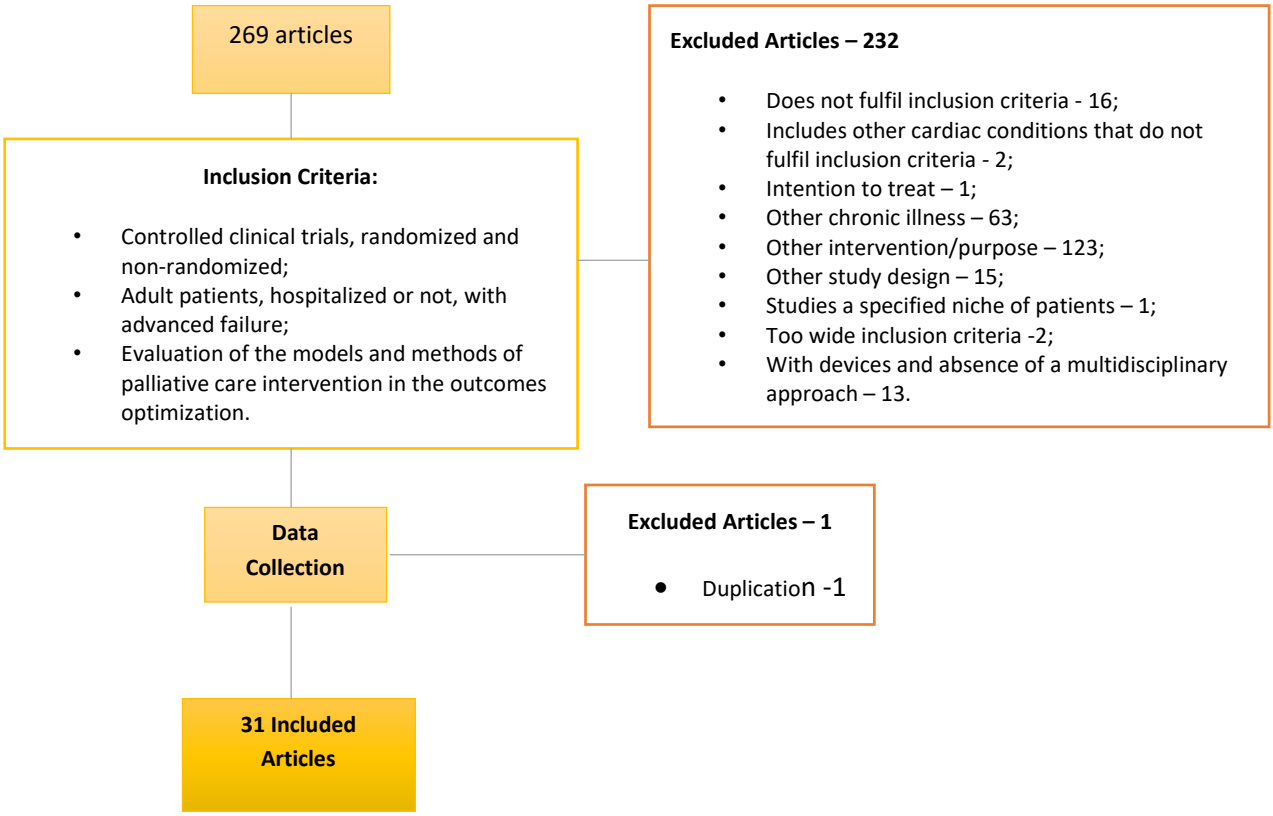

Figure 1: Figure 1: Flowchart (based on PRISMA chart) summarizing the stages of research.

The pool of 31 clinical trials regarding the integration of palliative care in heart failure therapy were registered between 2004 and 2018. The majority of the clinical trials (80,65%; 25) were registered after the year of 2010. Prior to that period, only four clinical trials were registered [Figure 11 in the annex]. Most part of the registered clinical trials were conducted in the US (10; 32,26 %) and in multiple countries of the European Community (12; 38,71%) [Table 6 in the annex].

Domain of Palliative Care Interventions

From the eight domains of palliative care defined, the ones that were a consistent focus of most of the clinical trials included in the revision were the domains concerning the management of physical and psychological symptoms. Around thirty percent of the trials provided interventions that were focused on end of life care /advance care planning and on addressing the patient and family social support needs. Nearly one fourth of the clinical

trials exhibited a palliative care component focused on providing education to the patient regarding his medical condition. Only a minority of clinical trials approached the spiritual and existential aspects of palliative care and worried about the continuous training and support of the elements of the interdisciplinary team.

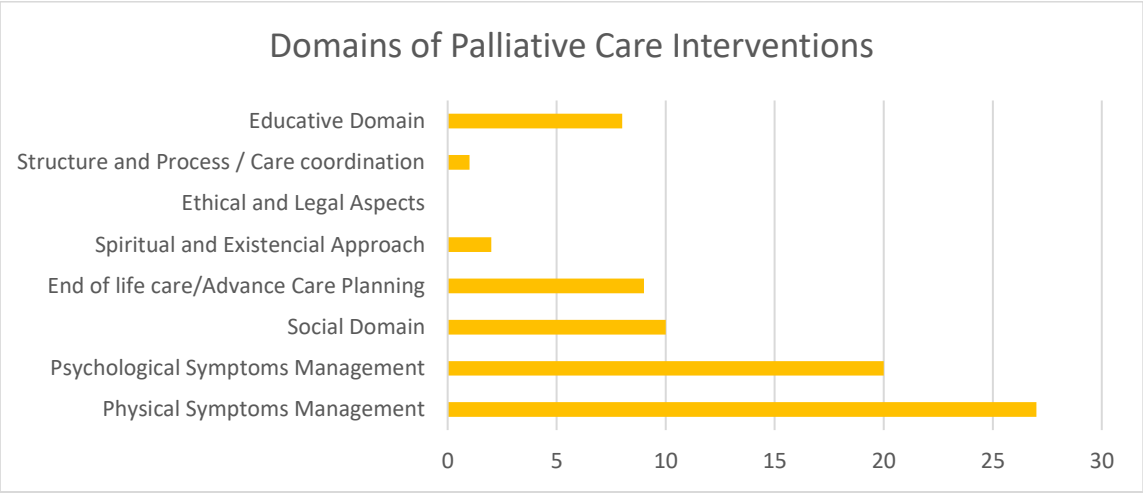

Figure 2: Number of clinical trials that contemplated each of the defined domains of palliative care.

Comparing the "earlier stages" and the "advance stages" groups in regarding to main domains covered by the palliative care interventions, both reveal a great focus in the management of physical and psychological symptoms. The group of "advance stages" distinguishes itself by the inclusion of end of life care/advance care planning and social component in the intervention.

Table 1: Relation between the criteria of inclusion regarding the NYHA staging of the patients and the domains of palliative care focused on the clinical trials interventions.

Domain of intervention	Earlier Stages (17)	Advance Stages (10)
Physical Symptoms Management	15; 88,24%	8; 80%
Psychological Symptoms Management	9; 52,94%	7; 70%
Both Physical and Psychological Symptoms Management	16; 94,12%	8; 80%
Social domain	3; 17,65%	5; 50%
End of life care / Advance Care planning	2; 11,11%	9; 69,23%
Spiritual and Existential Approach	3; 17,65%	5; 5%
Ethical and Legal Aspects	0	0
Structure and Process / Care Coordination	1; 5,88%	6; 60%
Educative Domain	5; 27,78%	2; 15,38%

Degree of Expertise

Regarding the degree of expertise, 19 of the trials (61,29%) were primary palliative care interventions, 11 (35,48%) were secondary palliative care interventions and one (3,23%)

was a tertiary palliative care intervention. From the total of the clinical trials, five (16,13%) had an intervention classified as physical rehabilitation care.

Table 2: Degree of expertise of the interventions of the clinical trial included in the revision.

Degree of Expertise of Palliative Care Intervention	Number of registered clinical trials
Primary	19
Rehabilitation care	3
Secondary	11
Rehabilitation care	2
Tertiary	1

From a chronological perspective, if we consider the last five years, 9,68% (3) of the registered clinical trials had secondary palliative care interventions against 25,81% (8) registered clinical trials which studied primary palliative care interventions.

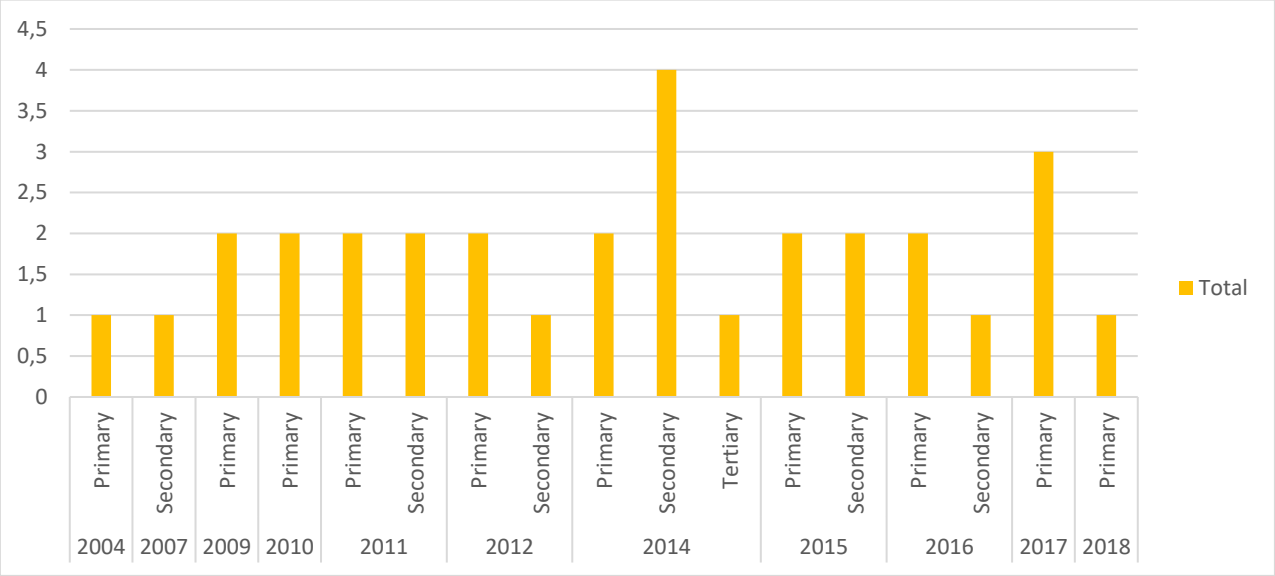

Figure 3: Chronological distribution of the registered clinical trials according to the degree of expertise of their palliative care intervention.

Regarding the proximity of the intervention in relation to the patient, most of the interventions (27; 87,1%) were instituted trough human contact. Two interventions (6,45%) were app-based. Seven (22,58%) of the clinical trials had interventions that implicated the regular use of the telephone. One trial (3,23%) had an intervention applied through the integration of all components, that is human contact, telephone and app.

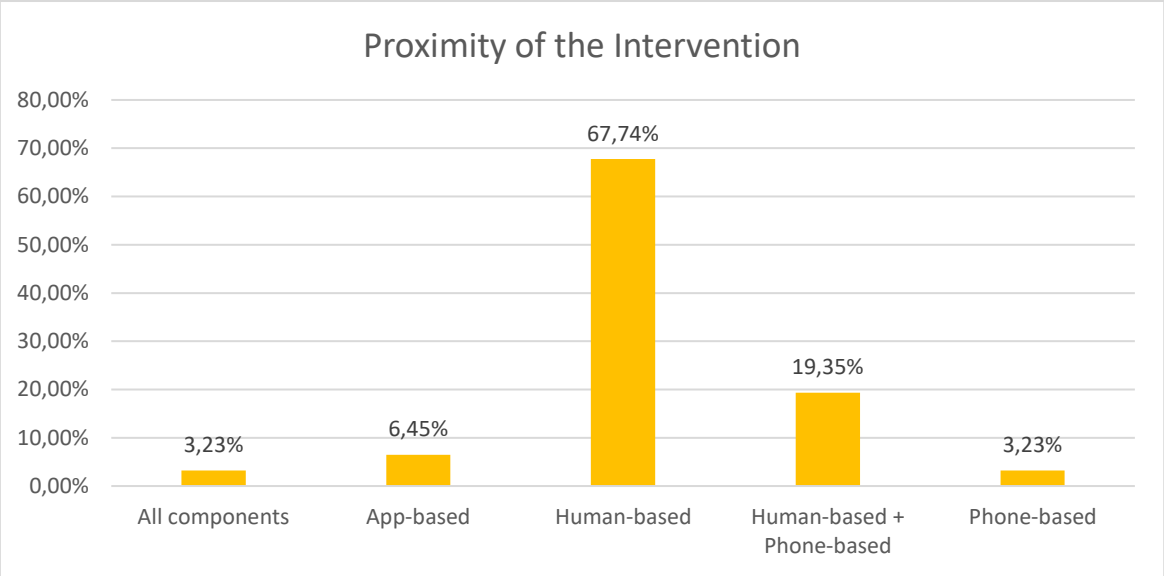

Figure 4: Proximity of the palliative care interventions of the clinical trials included in the revision.

Analyzing each group of degree of expertise, we can notice that 31,58% (6) of the trials with a primary palliative care intervention had an app-based or a phone-based component, whereas 68,42% (13) were exclusively human based interventions. From the group of secondary palliative care interventions, 36,36% (4) had a phone-based component, whereas 63,64% (7) were exclusively dependent on human contact. The soul tertiary intervention implicated exclusively a human component [Figure 11 in the annex].

When comparing the degree of expertise of the interventions and the timing of integration, we realize that, from the primary palliative care interventions, fourteen (73,68%) were inclusive to the "earlier" stages of heart failure and three (15,79%) exclusively directed to the "advance stages". From the secondary palliative care interventions, three (27,27%) were inclusive to the earlier stages against six (54,54%) directed to the advance stages. Each group had two clinical trials that did not specified the patients' stage of NHYA. The tertiary palliative care intervention was exclusively directed to advance stage patients.

Provider and Setting

Regarding the provider, fourteen clinical trials (45,16%) resulted from an interdisciplinary intervention (with more than one intervenient). Nine (29,03%) defined as main provider a nurse and one (3,23%) aimed to be provided by a social worker.

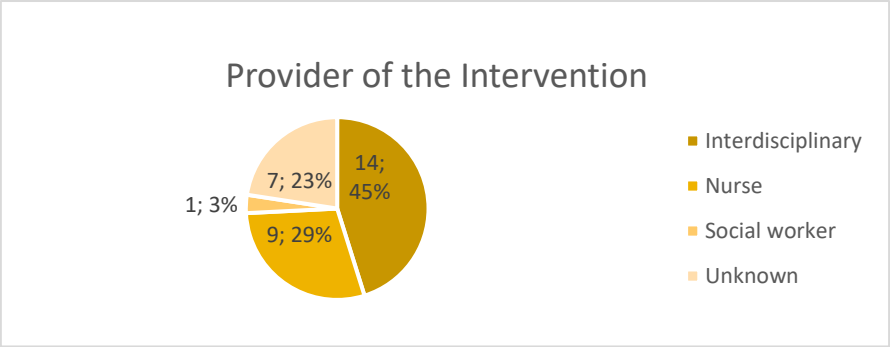

Figure 5: Distribution of the registered clinical trials according to its provider.

In what concerns the type setting of the intervention, eight (25,81%) were home-based interventions, fifteen (48,39%) only took place in an outpatient setting, six (19,35%) interventions combined home and outpatient settings and two clinical trials (3,23% for each setting) were respectively an hospice intervention and an intervention that combined the inpatient and outpatient setting. [Figure 12 in the annex].

The exclusive home base interventions were evenly distributed in what concerned the timing of integration (37,50%; 3 for each of the earlier and advance groups). From the interventions that took place in the outpatient setting, eleven (73,33%) were inclusive to patients in the earlier stages of the disease, whereas two (13,33%) were exclusively directed to the advance stages of HF. Both the interventions of the hospice setting and of a combination of the inpatient and outpatient settings were directed to advance stages. Regarding the trials that combined simultaneously the outpatient and home settings, they were equally divided between the earlier and advance groups (50%; 3 for each).

When comparing the setting of the palliative care intervention with its degree of expertise, we realized that from the group of primary interventions ten (52,63%) intended to be outpatient, six (31,58%%) were idealized for a home setting and three (15,79%) combined the outpatient and home settings. Considering the secondary palliative care interventions, there were five (45,45%) intended to be outpatient and there were three (27,27%) combining outpatient and home contexts. Two (18,18%) interventions were idealized for a home setting. There was one clinical trial which planned a simultaneous inpatient and outpatient palliative care intervention. The only tertiary palliative care intervention included in the study was designed for the hospice setting.

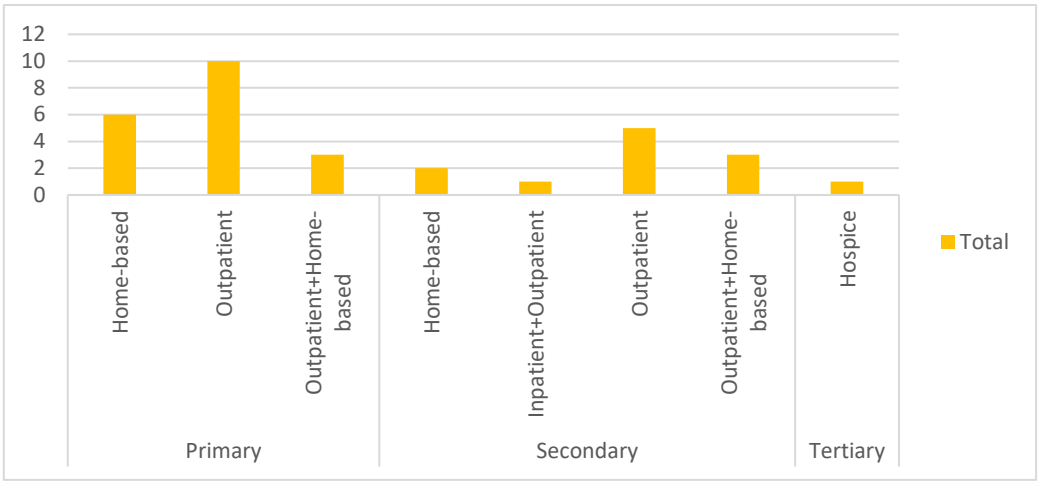

Figure 6: Relation between the setting and the degree of expertise of the palliative care interventions.

Outcome Measures

In this systematic review, we report an aggrupation of the primary and the secondary outcomes, since, in general, most clinical trials defined outcome measures focused on palliative care domains only on the secondary outcomes. However, a table regarding the assessment of the primary and the secondary outcomes in separated is provided in the table 7 of the annex. There was a big variability of outcome measures and of the applied assessment scales between the several clinical trials. In order to homogenize these differences for the analysis of the data, we defined groups of outcome measures by not specifying the scale applied and by solely referring the objective of the assessment scale in question, as shown in the following table.

Table 3: List of the most applied outcomes and respective number of clinical trials.

Outcome Measures	**Number of clinical trials that applied the outcome measure (N; %)**
QoL	26; 83,87%
Complaints of pain	7; 22,58%
Depression/anxiety	21; 67,74%
Pulmonary and Respiratory Function and Symptoms	15;48,39%
Cardiac Function and other laboratorial parameters	12; 38,71%
Complaints of oedeme and fatigue	13; 41,94%
Mortality parameters	7; 22,58%
Frequence of usage of health services	13; 41,94%
Emotional well-being	10; 32,25%
Goals of Care at end of life or Advance Care Directives	5; 16,13%
QoCommunication	1; 3,23%
Degree of disability	19; 61,29%
Adeherence to protocol	4; 12,90%

Patient understandement of prognosis and Perceived level of disease	4; 12,90%
Patient's degree of satisfaction	5; 16,13%
Patient’s self care hability	3; 9,67%
Patient's social limitations	14; 45,16%
Caregiver burden, mood, QoL	6; 19,35%
Treatment's adverse effects	10; 32,26%
Nutritional, sleep and health status	11; 35,48%
Cost-effectiveness of the intervention	5; 16,13%
Insigh on social support	2; 6,45%
Participation in decision making	1; 3,23%
Health Literacy	1; 3,23%
Time until medical optimization	1; 3,23%
Unknown	1; 3,23%

The most evaluated outcome measures were the patient’s quality of life (26; 83,87%), the application of depression/anxiety assessment scales (21; 67,74%) and the application of scales to assess the degree of disability (19; 61,29%). There was one clinical trial whose secondary outcome measures were not available.

The primary palliative care interventions are most focused on the assessment of the patient’s quality of life and the patient’s degree of disability and the assessment of symptoms of depression and anxiety. The secondary palliative care interventions had their main focus on the patient’s quality of life, the assessment of symptoms of depression and anxiety, the assessment of pain complaints and the determination of the frequency of usage of health care services. The only tertiary palliative care intervention included in the systematic revision was interested in assessing the patient’s quality of life, applying depression or anxiety assessment scales, evaluating the patient’s emotional well-being and the definition of goals of care at end of life or advance directives. This data is provided in the table 8 of the annex.

Comparators

All the thirty-one registered clinical trials included had control groups. Twenty-five (80,65%) of the clinical trials defined as control intervention the conventional heart failure therapy. The remaining clinical trials specified different control interventions.

Table 4: Type of control intervention defined by the included clinical trials.

Control Intervention	Number of clinical trials
Cardiac Resynchronization Therapy	1

Conventional therapy	25
Conventional therapy + aerobic training	1
Conventional therapy + routine rehabilitation training	1
Conventional therapy + Trimetazidine	1
Conventional therapy with low intensity inspiratory muscle training	1
Conventional therapy + Resistance exercise + health education	1

Status of Clinical Trials

More than half of the clinical trials (17; 54,84%;) were reported as completed, ten (32,26%) of the trials as recruiting and four (12,90%) as active but not recruiting.

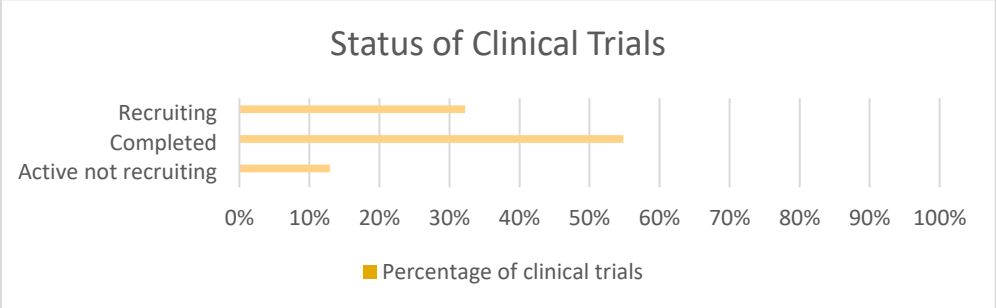

Figure 7: Graphic demonstrating the percentage of each status of the registered clinical trials included.

Study Design

In what concerns the study design, the model most applied was the parallel assignment (28; 90,32%). A total of two clinical trials were respectively a crossover assignment and a factorial assignment (3,23% each) and one (3,23%) was misclassified as a single group assignment, as it had a control group.

Table 5: Type of study design of the registered clinical trials included.

Study Design	Number of clinical trials
Crossover Assignment	1
Factorial Assignment	1
Parallel Assignment	28
Single Group Assignment	1
Total Geral	**31**

Sample's Characteristics

Considering the clinical trials that reported information concerning the sample's size, there was a total of 4074 patients and the median of participants estimated to be enrolled in each trial was 82 and the first inter-quartile was 57,5.

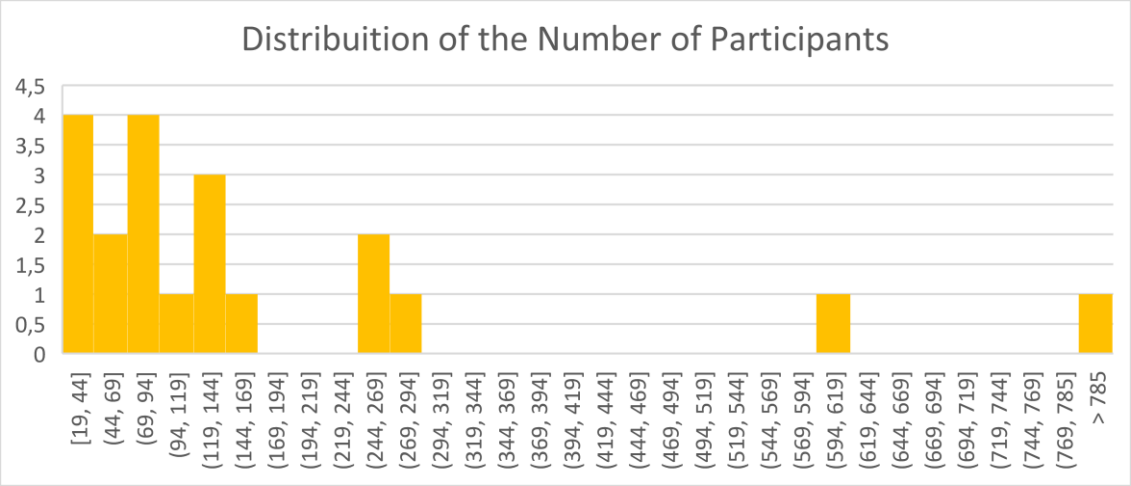

Figure 8: Histogram showing the distribution of the number of participants.

Most of the trials (22; 70,97%) had a target population mainly from 18 to no maximum limit age. Two (6,45%) of the trials did not established age limits. Three clinical trials aimed to be exclusively directed to elderly, that is over 65 years of age.

Publications

From the included studies, sixteen (51,61%) were published and 75% of those publications occurred since 2015.

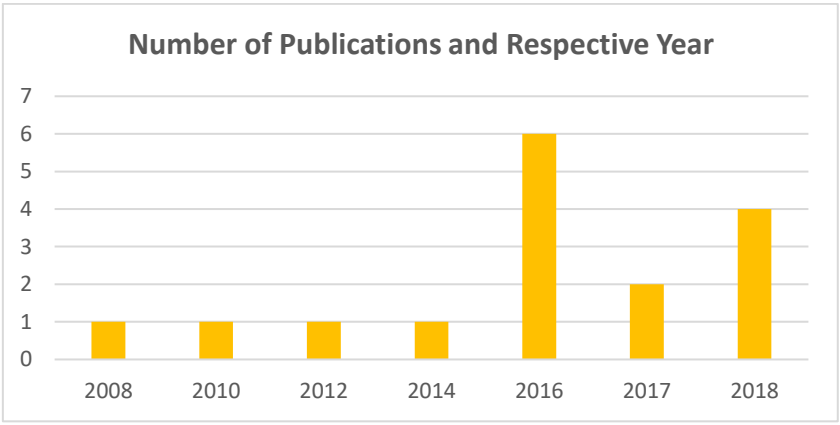

Figure 9: Graphic showing the number of registered clinical trials publications throughout the years, whereas 75% were published after 2015.

From the group of non-published clinical trials, ten (66,67%) were on status of recruiting (8; 53,33%) or active, not recruiting (2; 13,33%) and five (33,33%) had a completed status. If we consider the year of last update in the data base, ten (66,67%) of the non-published clinical trials were last updated longer than two years ago. To note that one of

the registered clinical trials with completed status, despite the absence of publication, uploaded the results obtained in the clinicaltrials data base.

Most of the clinical trials published took place in the US and in Brazil (4;25% each). A total of five (31,25%) publications came from countries from the European Union [Table 9 in the annex].

After analyzing the degree of expertise of the published clinical trials, there is to note that 56,25% (9) were primary palliative care interventions and 43,75% (7) corresponded to secondary palliative care interventions [Table 10 in the annex].

Discussion

Thanks to the advances in heart failure treatments, that resulted from the emergence of new medicines, the improvement of pharmacological management, better coronary revascularization techniques and circulatory and electrical devices, the longevity of heart failure patients was significantly increased. However, heart failure care continues to be challenged by symptomatic recurrence, high rates of mortality and hospital readmissions and, consequently, a disproportioned rhythm of improvement of the patient's quality of life given the treatment advances (34) (35) (36) (37) (38). Despite the heart failure population being a deserving and adequate target for palliative care management (39), this care is scarcely implemented in this context (26) (40) (41) and there is also a great delay in its access (42) (43). We recognize the challenge in the heart failure patients' referral to palliative care (44), due to the non-linear trajectory of the disease (45) (46), the difficulty to estimate a reliable prognostic (47), the lack of coordination between the specialties of heart failure and palliative care (48) and misinformation of the patients regarding palliative care (49).

The early integration of palliative care has been strongly recommended, for the fact that it can lead to an improvement of quality of life by helping the patients and their families and their caregivers in the process of coping with the disease, in the symptoms management, and in decision-making (29) (50) (51) (34) (52) (53) (54) (55) (56). In Delphi consensus several experts assessed the time of referral according to prognosis, time from diagnosis, treatment trajectory and performance status and pointed out that sometimes referral can be made too early in the course of the disease (57). Therefore, a revision on the subject advocates for timely palliative care, trough the selection of the right patient

for the right level of intervention at the right time, rather than universal early palliative care referral (31).

Considering that since 2017 there were only registered clinical trials studying basic palliative care interventions, there seems to exist a focus on primary palliative care interventions. This phenomenon might arise from the recent evidence supporting an early referral to palliative care, since in the earlier stages of the disease there is no great complexity in the heart failure care, being basic palliative care enough for symptoms management and patients' education concerning their disease. That is reflected on the fact that around 73,68% of the primary palliative care interventions are inclusive for earlier stages of heart failure against the 27,27% observed in the secondary palliative care interventions. Another reason is that basic palliative care can be more easily accessed by a closer approach to the patient, notably the home-base approach. In fact, if we assess the proportions of clinical trials that had a exclusive home-based approach, we obtain 31,58% for the primary palliative care interventions against the 18,18% for the secondary palliative care interventions.

Given the different aims of this supportive care, ideally, it should be provided by an interdisciplinary team consisting of a physician, a nurse and a psychosocial team member (58), since there seems to exist a tendency of better outcomes improvement in studies involving interdisciplinary teams in comparison to nursed-led palliative care (9) (11) (59) (60) (61) (62) (63). In fact, the interdisciplinary nature of palliative care is crucial to address the multidimensional supportive care needs of patients with advanced chronic illness. The permanent cooperation between the different professionals in specific times, according to the patient's needs, allows the focus on the most affected patients' dimensions. However, less than half (45,16%; 14) of the clinical trials provided an interdisciplinary intervention, which can result from the difficulty to rearrange a complete team, due to the lack of human resources and difficulty to assure the communication between all the elements.

Most of the clinical trials provided palliative care interventions focused on the domain of symptom management. Advance heart failure patients most frequent complaints concern fatigue, oedeme of the extremities and respiratory difficulties (64). However, these symptoms were considered as outcome measures, respectively, only in thirteen (41,94%) and fifteen (48,39%) clinical trials. There is a high prevalence of emotional distress and

depression in the heart failure population, which has been linked to higher risk of hospital readmission or death (65) (66) (67). This fact justifies a continuous search for these symptoms during the course of the disease, in order to enable a competent therapeutic response. In accordance to this perspective, the assessment of symptoms of depression and anxiety is the third (21; 68%) most frequent outcome measure appraised by the total of clinical trials.

The communication between heart failure patients and their providers concerning prognostication, expectations of illness trajectory, therapeutic approaches available and advance care planning is frequently deficient (39) (68). In fact, only nine (29,03%) clinical trials developed interventions aimed at this domain. This can mainly be due to the absence of a defined adequate moment for engaging in goals of care conversations (69) and also, to the misaligned patient's perception of the prognosis and overestimation of their life expectancy in comparison to the one estimated by their health provider (70).

Another important domain of palliative care, focused just on eight (25,81%) clinical trials, concerns the reinforcement of patient's education regarding the physiological and clinical aspects of their disease, self-care behaviors and the promotion of the patients' compliance to the treatment measures. This pedagogic intervention has shown benefits by reducing hospital readmissions and costs of care (71) (72) and is a way to empower the patient, giving them some control over his illness and, therefore, improving clinical outcomes, such as emotional distress and quality of life (73).

There were ten (31,26%) clinical trials whose interventions were focused on the patients' social environment, either by including the caregivers and/or family members in the intervention itself or in the period post-intervention or by promoting the socialization and experience sharing with other heart failure patients. Nine (29,03%) promoted the inclusion of caregivers and/or family members, showing the importance of these agents, who, not only have an inherent burden secondary to the disease implications over the family setting, but also are an important patient's source of social support, which has been proven to be linked with adapting coping skills and better self-care (74). Moreover, there were six (19,35%) clinical trials that aimed to assess the caregiver's burden, mood and quality of life. Concerning the outcomes measures, the number of trials that examined the

patients' insight on their social support were markedly reduced, corresponding to two (6,45%) trials. There were fourteen (45,16%) trials that assessed the existence of social limitations arising from heart failure disease.

Implications for Practice

The data from this systematic review showed important heterogeneity of the palliative care interventions, being not yet possible to define the most efficient model to provide this type of care in the treatment of heart failure. However, it seems that the efficiency of this care will reside in its individualization to the patients' and family members' expectations and desires. Evidence is lacking on this subject and the data collected reveals that most of the interventions still do not follow the recent recommendations regarding palliative care, notably the interdisciplinary approach, the promotion of shared decision-making with the patient and its family, the improvement of the patient health literacy (7) and also several technical and structural aspects regarding the choice outcomes measures, the score used to asses them and the monitoring of their change over time (75). Therefore, is important to better define some orientations, particularly the core set outcomes for this area, in order to facilitate the comparison of results.

Limitations

Firstly, there were only considered the clinical trials registered in the clinicaltrials.gov; WHO ICTRP; clinicaltrialsregister.eu; ISRCTN registry. As a consequence, it is important to point out that the policy of mandatory registration of clinical trials was implemented in 2007 (76) and that the clinicaltrials.gov database was only launched in September 2008 (77). Secondly, there was some data missing or not submitted regarding the outcomes assessed and the characteristics of the interventions. Finally, there was a great heterogeneity of the models of intervention and the outcomes assessed, which lead to a simplified comparison of the several clinical trials and the inability to compare the results submitted by some of the clinical trials.

Conclusion

Given that 75% of the publications occurred since the year 2015, this suggests a recent popularity of the matter discussed. It was also demonstrated a recent interest in primary palliative care, which can be explained by the recent recommendations supporting earlier

palliative care. The most popular settings were the outpatient setting and home setting or a combination of both and the human contact was privileged. The several palliative care interventions revealed a great variability of outcomes and exhibit a great heterogeneity in method and type of palliative care intervention provided. The main domain of palliative care targeted by most of the trials was the management of symptoms. The group of "advance" stages revealed a higher inclusion of end of life care/advance care planning and social component in the interventions provided. Concluding, there is currently a shift in the palliative care approach in the management of heart failure, with a tendency of a greater focus on an earlier implementation of this type of care.

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Annex

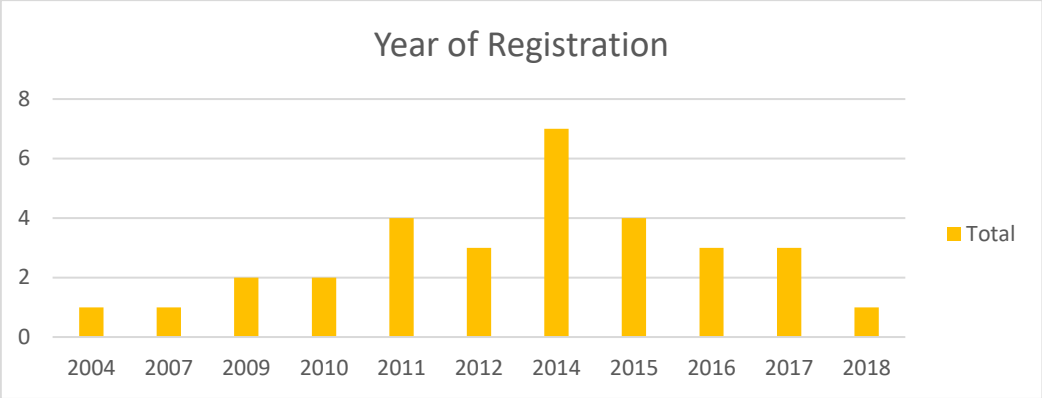

Figure 10: Temporal evolution of the registration of the clinical trials included in the systematic review. The majority of the clinical trials were registered after 2010, whereas more than half (57,14%) of the clinical trials were registered in the last six years

Table 6: Number of registered clinical trials pear country.

Country	Number of clinical trials registered
Belgium + Denmark + Germany + Italy +Luxembourg +Netherlands +Norway	1
Belgium + Italy	1
Brazil	4
China	3
Denmark	1
Greece	2
Libane	1
Poland	1
Portugal	1
Singapore	1
Spain	2
Sweden	2
United Kigdom	1
USA	10
Total	**31**

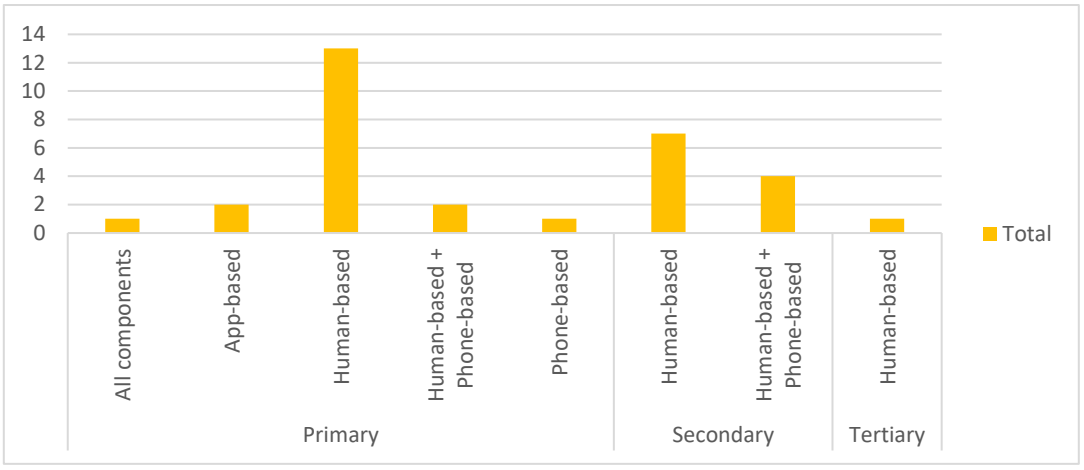

Figure 11: Graphic showing the relation between the degree of expertise of the palliative care interventions and their respective proximity.

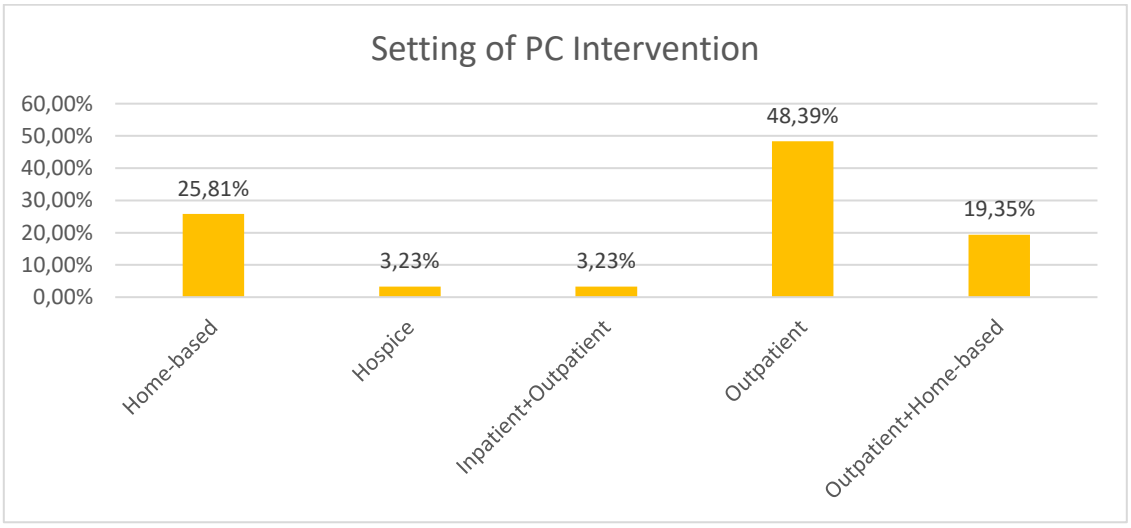

Figura 12: Distribution of the clinical trials according to the setting where the palliative care intervention is provided.

Table 7: List of the most commonly applied primary and secondary outcomes and number of clinical trials.

Outcome Measure	**Clinical trials that applied the outcome measure as primary outcome (N; %)**	**Clinical trials that applied the outcome measure as secondary outcome (N; %)**
QoL	10; 32,25%	18;58,06%
Complaints of pain	3; 9,67%	4; 12,90%
Depression/anxiety	7; 22,58%	15;48,39%
Pulmonary and Respiratory Function and Symptoms	7; 22,58%	12; 38,71%
Cardiac Function and other laboratorial parameters	3; 9,67%	11; 35,48%
Complaints of oedeme and fatigue	3; 9,67%	10; 32,25%
Mortality parameters	8; 25,81%	1; 3,23%
Frequence of usage of health services	5; 16,12%	9; 29,03%
Emotional well-being	4; 12,90%	6; 19,35%
Goals of Care at end of life or Advance Care Directives	2; 6,45%	3; 9,67%

QoCommunication	1; 3,23%	0
Degree of disability	7; 22,58%	18; 58,06%
Adeherence to protocol	1; 3,23%	4; 12,90%
Patient understandement of prognosis and Perceived level of disease	1; 3,23%	4; 12,90%
Patient's degree of satisfaction	0	5; 16,12%
Patient’s self care hability	2; 6,45%	1; 3,23%
Patient's social limitations	4; 12,90%	10; 32,25%
Caregiver burden, mood, QoL	2; 6,45%	5; 16,12%
Treatment's adverse effects	2; 6,45%	8; 25,81%
Nutritional, sleep and health status	0	11; 35,48%
Cost-effectiveness of the intervention	0	5; 16,12%
Insigh on social support	0	2; 6,45%
Participation in decision making	0	1; 3,23%
Health Literacy	0	1; 3,23%
Time until medical optimization	0	1; 3,23%
Unknown	0	1; 3,23%

Table 8: Shows the percentage of application of the outcome measures according to the degree of expertise of the palliative care interventions.

Outcome Measures (Primary and Secondary)	**Intervention's Degree of Expertise**		
	Primary	**Secondary**	**Tertiary**
QoL	17	8	1
Complaints of pain	1	6	0
Depression/anxiety	12	8	1
Pulmonary and Respiratory Function and Symptoms	10	5	0
Cardiac Function and other laboratorial parameters	10	2	0
Complaints of oedeme and fatigue	10	3	0
Mortality parameters	6	2	0
Frequence of usage of health services	7	6	0
Emotional well-being	5	4	1
Goals of Care at end of life or Advance Care Directives	2	2	1
QoCommunication	1	0	0
Degree of disability	14	5	0
Adeherence to protocol	3	1	0
Patient understandement of prognosis and Perceived level of disease	2	2	0
Patient's degree of satisfaction	2	3	0
Patient’s self care hability	0	2	0
Patient's social limitations	10	4	0
Caregiver burden, mood, QoL	3	3	0
Treatment's adverse effects	9	1	0
Nutritional, sleep and health status	8	3	0
Cost-effectiveness of the intervention	4	1	0
Insigh on social support	1	1	0
Participation in decision making	0	1	0
Health Literacy	1	0	0
Time until medical optimization	1	0	0
Unknown	0	0	0

Table 9: Number of publications pear country.

Country	Number of Publications
Singapore	1
Belgium + Denmark + Germany + Italy +Luxembourg +Netherlands +Norway	1
Brazil	4
China	1
Denmark	1
Greece	1
Libane	1
Spain	1
Sweden	2
USA	4

Table 10: Shows the relation between the degree of expertise of the palliative care interventions, the status of the clinical trials in question and its publication status. From the non-published clinical trials with primary palliative care interventions 30% (3) had a completed status whereas 70% were on recruiting (6) or active, but not recruiting status. (1). From the group of non-published clinical trials with secondary palliative care interventions 60% (3) were already completed against 40% (2) of clinical trials which were on recruiting status.

Relation between degree of expertise of the interventions, status of the clinical trial and publication	Number of Clinical Trials
Primary	**19**
No	**10**
Active, not recruiting	1
Completed	3
Recruiting	6
Yes	**9**
Active, not recruiting	1
Completed	6
Recruiting	2
Secondary	**11**
No	**4**
Completed	2
Recruiting	2
Yes	**7**
Active, not recruiting	1
Completed	6
Tertiary	**1**
No	**1**
Active, not recruiting	1